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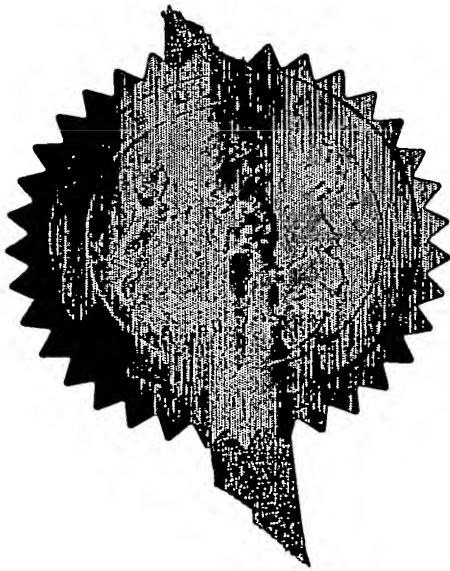
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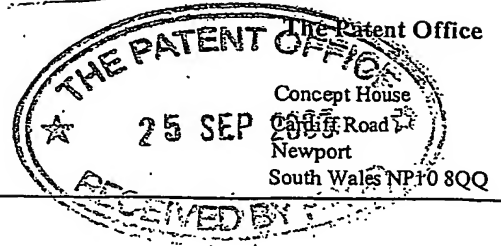
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Title of the invention

METHOD AND APPARATUS FOR MASS SPECTROMETRY

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METHOD AND APPARATUS FOR MASS SPECTROMETRY

The present invention relates to mass spectrometry and, more particularly, to the scheduling of the steps involved in performing mass spectrometry. The present invention will be of particular benefit to types of mass spectrometry that generate large quantities of data and hence give rise to lengthy data-processing. Examples of data-rich spectrometry include quadrupole time of flight (QTOF), nuclear magnetic resonance (NMR) and Fourier transform Orbitrap (FT-O). Details of an Orbitrap system can be found in US Patent No. 5,886,346.

High-resolution mass spectrometry is widely used in the detection and identification of molecular structures and the study of chemical and physical processes. A variety of different techniques are known for the generation of mass spectra using various trapping and detection methods. The present invention is applicable to many of these techniques.

One such technique is Fourier Transform Ion Cyclotron Resonance (FT-ICR). FT-ICR uses the principle of a cyclotron, wherein a high-frequency voltage excites ions to move in a spiral within an ICR cell. The ions in the cell orbit as coherent bunches along the same radial paths but at different frequencies, the frequency of the circular motion (the cyclotron frequency) is proportional to the ion mass. A set of detector electrodes are provided and an image current is induced in these by the coherent orbiting ions. The amplitude and frequency of the detected signal are indicative of the quantity and mass respectively of the ions. Mass and frequency spectra are obtainable by carrying out a Fourier Transform of the

'transient', i.e. the signal produced at the detector's electrodes.

Figure 1 shows a known mass spectrometer 10, that is operated as follows. Samples are prepared in an optional sample preparation stage 12 with ions being generated in an ion source 14 before being stored in an ion trap 16. When desired, the ions are transmitted to an ion cyclotron resonance (ICR) cell 20 via ion optics 18. The ion transmission and capture in the ICR cell 20 can occur via two well-known schemes: gated trapping or continuous trapping. The ions in the ICR cell 20 are excited by a radio-frequency signal provided by an excitation system 22 operated under the control of a distributed computer system 26. The transient is detected by detection hardware 24 (amplifiers and other analog circuitry) before being digitized at 28 and passed to the control computer 30. When a complete signal has been detected by the hardware 24, the transient data are either sent directly to the user data system 32 for storage or is processed by the control computer 30 to produce frequency or mass spectra peaks lists. Any combination of transient data can be displayed. In addition, simple decisions for controlling the next data acquisition cycle are possible where the transient data are processed. A more detailed description of an FT-ICR spectrometer can be found in our co-pending Patent Application No. GB0305420.2.

The method of operation of the mass spectrometer of Figure 1 can be simply summarized as shown in Figure 2.

The steps are as follows:-

- (i) ionization in the ion source at 34;
- (ii) ion collection and preparation in the ion

trap at 36;

(iii) ion transmission to the ICR cell at 38;

(iv) ion detection in the ICR cell (i.e.
transient data collection) at 40;

5 (v) processing of the transient data at 42; and

(vi) storage of the processed data at 44.

Once storage step 44 has been completed, a new cycle may begin with ionization step 34 followed by sample preparation step 36 as possibly modified by the results
10 of the transient data processing step 42 of the previous cycle. Often, the processing step at (v) is omitted and instead the data collected at step (iv) is merely dumped direct to a computer disk. The time taken for each step/steps is shown in Figure 2. As can be seen the
15 longest steps are for data detection and data processing 40 and 42, and these steps are performed successively. This is because the data collected in one cycle, once processed, may be used to control the ion collection and preparation in the following cycle.

20 Against this background, and from a first aspect, the present invention resides in a method of mass spectrometry comprising a plurality of cycles, each cycle comprising the steps of: (a) preparing ions to be analysed by a mass spectrometer; (b) using a detector of
25 the mass spectrometer to collect data from the ions prepared in step (a); and (c) processing the data collected in step (b) with processing means; wherein at least a part of step (a) and/or (b) of a cycle is performed concurrently with step (c) of the previous
30 cycle.

By performing certain steps of one cycle concurrently with steps of the previous cycle, greater

overall efficiency can be achieved. The benefit is great because the two most time-consuming steps - ion detection and data processing - are performed in parallel. As the two steps are wholly independent of one another, there is
5 no conflict in operating the steps concurrently.

To date, the delay inherent in performing steps (a), (b) and (c) successively has not posed a problem and has become the standard that is adopted unquestioningly. However, we have appreciated that considerable benefits
10 can be enjoyed using parallel operating in new techniques such as chromatography in Fourier transform mass spectrometers. In chromatography, any delay between ion preparation for each cycle is undesirable as it causes uncertainty as to whether a parent ion is still present.

15 The ion "preparation" of step (a) should be construed broadly and may comprise any of ion generation, ion handling (e.g. ion fragmentation, selective accumulation of ions, electrospray injection (ESI), and matrix-assisted laser desorption of ions (MALDI)), ion
20 trapping and transmission of ions to an ICR cell or the like. Data collection using a detector at step (b) corresponds to ion detection within an ICR cell or other suitable detector and may comprise detecting a transient in an ICR cell, as described previously. Data processing
25 at step (c) corresponds to manipulation of the data collected at step (b) rather than mere data collection. For example, this data processing may comprise obtaining a Fourier transform of the transient to obtain a mass spectrum and/or processing the data to allow storage in a
30 reduced form (e.g. rather than storing an entire mass spectrum, just information relating to the peaks may be stored). The processing means may form part of the mass

detector, such as a processor chip located in a control panel, but is a separate entity from the detector.

Alternatively, the processing means may be physically separate from the mass spectrometer, e.g. a personal
5 computer connected to the mass spectrometer by a serial cable or the like.

Optionally, the method may comprise the step of starting step (a) of a cycle upon completion of step (b) of the previous cycle. This may be immediately upon
10 completion or after a short delay. Alternatively, the method may comprise the step of starting step (a) of a cycle during step (b) of the previous cycle. In this latter case, the method may optionally comprise the step of starting step (b) of a cycle upon completion of step
15 (b) of the previous cycle, such that each data collection step (b) is performed sequentially. Preferably, the method comprises the step of controlling step (a) and/or step (b) of a cycle in response to data processed in step (c) of a previous cycle. This allows experiments to be
20 tailored to results obtained in initial scans.

Optionally, step (b) may further comprise making available a sample of data collected during an initial period thereof for processing in step (c) while the remainder of the data collection of step (b) continues.
25 Preferably step (a) and/or step (b) of a cycle is controlled in response to a sample of data processed in step (c) of a previous cycle. The sample of data may have been collected in the immediately preceding cycle. The method may be used with a hybrid spectrometer comprising
30 first and second detectors. In this case, the method may further comprise the step of injecting ions into the first detector from the second detector in response to a

sample of data processed in step (c). In addition, injection may be made in response to a signal from the first detector as well. The first detector may be part of the ion trap and the second detector may be part of the ICR cell. The ICR cell may be used for FT-ICR data collection. Alternatively, the second detector may be a mass spectrometer configured to perform time-of-flight experiments. A further alternative is for the first and second detectors to be part of separate static traps, i.e. traps that use static electric and/or magnetic fields, or hybrid mass spectrometers such as trap-Orbitrap or Orbitrap-Orbitrap devices.

According to a second aspect, the present invention resides in a method of mass spectrometry comprising a plurality of cycles, each cycle comprising the steps of: (a) preparing ions to be analysed with a mass spectrometer; (b) using the mass spectrometer to collect data from the ions prepared in step (a); and (c) processing data collected in step (b); wherein a sample of the data collected during an initial period of step (b) is processed concurrently with the remainder of the data collection of step (b) and is used to control step (a) and/or step (b) of a subsequent experiment.

By 'experiment' we mean a sequence of ion preparation and ion detection. This experiment may correspond to another full cycle or may merely be a part of a cycle. For example, a single cycle may comprise a plurality of experiments, each experiment involving its own ion preparation and detection procedures, but where the data is collected together and processed as a whole within that single cycle.

Optionally, the sample of data is collected in an ICR cell and, once processed, is used to control step (a) and/or step (b) of a subsequent experiment performed in an ion trap concurrently with collection of the remainder
5 of the data in the ICR cell. Preferably, a full mass spectrometry scan is collected in the ICR cell and a MS^n scan is collected in an ion trap. For example, in one cycle a mass spectrometry scan may be collected in the ion trap and, based upon a sample of data, a series of MS^n
10 scans may be taken in the ion trap timed so as to complete at around the same time as completion of data collection in the ICR cell. Optionally at least step (a) and/or step (b) of a cycle is performed concurrently with step (c) of the previous cycle.

15 In order that the invention may be more readily understood, reference will now be made, by way of example only, to the accompanying drawings in which:

Figure 1 is a simplified representation of a known mass spectrometer;

20 Figure 2 is a method of operating the mass spectrometer of Figure 1;

Figure 3 is a simplified representation of a mass spectrometer suitable for use with the method of the present invention;

25 Figure 4 shows a method of mass spectrometry according to a first embodiment of the present invention;

Figure 5 corresponds to Figure 4, but shows a method of mass spectrometry according to a second embodiment of the present invention;

30 Figure 6 corresponds to Figure 5, but for a case with a short ion preparation time;

Figure 7 corresponds to Figure 4, but shows a method of mass spectrometry according to a third embodiment of the present invention;

Figure 8 shows an example time line for illustrating
5 a method of mass spectrometry according to a fourth embodiment of the present invention; and

Figure 9 corresponds to Figure 4, but shows a method of mass spectrometry according to a fifth embodiment of the present invention.

10 A mass spectrometer suitable for use with the present invention is shown in Figure 3. Many parts correspond to those of the mass spectrometer of Figure 1 and so like reference numerals (but incremented by 100) are used to label like parts. Accordingly, Figure 3
15 shows a mass spectrometer 110 that operates under the control of a user data system 132 and a system control computer 130 that may be used to control sample preparation at 112. Samples are ionized in an ion source 114 before being transferred to the ion storage devices
20 116 and 117 that may be, for example, ion traps or ion stores. Depending upon the relative ion capacities of the ion storage device 116 and the ICR cell 120, an intermediate ion storage device 117 may be used to buffer prepared ions from multiple cycles of the ion storage
25 device 116 prior to injection as well-defined packets into the ICR cell 120 via ion optics 118. The ICR cell 120 is optimized for detection of the packets of ions, but it may also be used to perform other ion manipulation such as ion fragmentation through techniques like
30 election capture dissociation (ECD) or infrared multi-photon dissociation (IRMPD) prior to detection.

The detect cycle in the ICR cell 120 is controlled by computer 128 that uses analog, A/D and D/A circuitry 125, as well as amplifiers both for excitation of the ions and for processing the transient data collected.

5 After gated trapping and a short switching delay (a few ms), ions are excited by a radio frequency signal that is calculated by the computer 130 and transmitted via D/A circuitry 125 and amplifier 122. Typical durations of the excite waveform are 5ms to 20ms. After a short delay

10 (the recovery time of the detect hardware of the excitation), the excited ions in the ICR cell 120 are detected by electrodes (not shown): the signal they produce is amplified at 124 and digitized at 125. The computer 128 can start processing the transient data

15 immediately, i.e. even while data acquisition continues. Information from computer 128 may be communicated with the system control computer 130 and/or can be stored directly in the user data system 132.

Figure 4 shows a method of operating the mass spectrometer of Figure 3 in accordance with a first

20 embodiment of the present invention. Three cycles 1, 2, 3 of data capture and processing are shown side-by-side in Figure 4: time is represented approximately in the vertical direction such that relative timings between

25 cycles 1, 2, 3 can be inferred. Moreover, the height of the boxes are approximately proportional to the time taken for the step they represent. Corresponding steps within each cycle are labeled by a common reference numeral, with a subscript denoting the cycle to which

30 they belong.

For the sake of clarity, the ionization, preparation, storage and transmission steps are shown as

a single box labeled 150. At the start of the first cycle, ions are collected and prepared at 150 before transmittal to the ICR cell 120 where the detection step 152 can start. Once a full detection scan has completed, the data collected is processed at 154₁ and, conveniently, ions are prepared and collected in the second cycle at 150₂ ready for transmission to the ICR cell. Data collection for the second cycle can then start: the data collection 152₂ will start whilst the data collected during the first cycle at 152₁ is being processed at 154₁ because the ion collection, preparation and transmission step 150₂ takes less time than the data processing step 154₁. Once the data has been processed in the first cycle 154₁, it can be stored at 156₁ in the user data system 132: generally this step occurs concurrently with the ion detection step of the second cycle 152₂.

As will be clear from Figure 4, once the data has been processed at 154₁, it is used by the system control computer 130 to decide at 158₁ whether or not to continue obtaining data and, if continuing, how any of the ion collection, ion preparation 150 or ion detection steps 152 proceed. As mentioned above, the ion collection, preparation and transmission steps of the second cycle all occur before the data processing step of the first cycle 154₁ is complete. In addition, the data collection step of the second cycle 152₂ begins before the data processing step of the first cycle 154₁ is complete. As a result, the data processing step of the first cycle 154₁ can be used to influence the operation of only the third and subsequent cycles.

It will be clear that the description above is couched in terms of the first and second cycles but

applies equally well to the second and third cycles, the third and fourth cycles, and so on.

A typical sequence of ion collection, preparation
150 and detection 152 and data processing 154 takes
5 around 1s. Depending upon the samples and the desired
mass resolution, the detect time can be shortened
significantly. The data processing step 154 increases in
time as the mass range increases or the amount of data
increases.

10 Figure 5 shows an alternative embodiment of the
present invention. Much detail is shared with the
embodiment of Figure 4 and so common reference numerals
are used where appropriate. In addition, descriptions of
like parts will not be repeated here for the sake of
15 brevity. In this second embodiment, the overlap of
successive cycles 1, 2, 3, 4 is greater because one cycle
is started whilst the ion detection step of the previous
cycle is still in operation. This is achieved by
generating, preparing and storing ions whilst data
20 collection of the previous cycle continues. The stored
ions for the following cycle are ready for transmission
as soon as the data detection step of the previous cycle
is complete. Using such a method, steps from three or
even four successive cycles may all be in operation in
25 the mass spectrometer 110 in any one instance. For
example, the data from the first cycle may be written to
the store at 156 whilst the data from the second cycle is
being processed at 154, whilst the data from the third
cycle is being detected at 152, whilst the ions in the
30 fourth cycle are being collected and prepared 150. Such
an arrangement is shown in Figure 5 for the most
advantageous case where ion preparation 150, detection

152 and data processing 154 all require approximately the same amount of time. This would correspond to a case, for example, where a low ion current is produced by the ion source 114 and the ions are isolated and fragmented in a RF ion trap 116 with a mass range of interest from 100 to 1,000 with a desired resolution of 100,000 at 400. This would lead to approximately equal ion preparation 150, detection 152 and data processing 154 steps of around 0.7s.

At a first glance, this second embodiment looks superior to the first embodiment in that the parallel processing is optimized. However, there is a disadvantage in that the increased efficiency means that data processed in the first cycle at 154₁ cannot be used to influence any cycle before the fourth and subsequent cycles.

In real systems, the duration of the ion preparation 150, detection 152 and data processing 154 steps can vary relative to each other, such that one may be far longer than the others and so will be rate determining. The relative timing of each step must be accounted for by the decision processes 158 and may require the system control computer 130 to delay ionization or prolong storage of the ions where, for example, the ion preparation time 150 is short compared to the ion detection time 152. With some timing schemes, the data from the first cycle 154₁ can be used to influence ion preparation 150₃ in the third cycle, as illustrated in Figure 6.

Figure 7 shows a third embodiment of the present invention that incorporates a modification to the ion detection 152 and data processing 154 steps. Usually,

the data acquisition parameters are set before the start of a cycle, with that cycle being implemented as pre-determined. Ion detection 152 is performed for the pre-determined time and only then is a Fourier Transform
5 taken (for the case of FT-ICR) at 154. The duration of the detection step 152 determines the resolution that may be achieved (and is proportional therewith). As will be appreciated, the transient data is collected continually during the ion detection step 152. A typical transient
10 size is 1024 ksamples: this high number allows high resolution with simultaneous detection of low masses.

Rather than waiting for the entire ion detection step 152 and data processing step 154 to complete before a decision 158 can be made as to how, or if, to adapt
15 subsequent ion preparation 150, ion detection 152 or data processing steps 154; a sample from the start of the transient is processed immediately at 160₂ whilst the rest of the ion detection step 152₁ continues. Although the statistics are reduced in proportion to the brevity of
20 the sample, any length of sample can be processed to generate a low-resolution mass spectrum, as indicated at 160₂ of Figure 7. Although resolution will be degraded, it is adequate for assessing how the next cycle is to be performed or whether a sequence of scans are to be
25 aborted.

In this embodiment, the first 32ksamples of transient data are used in the decision process 160₂. However, the length of the sample can be varied within the timing constraints of the series of cycles. It may
30 be that the sample of data is not particularly small in relation to the whole of the data. Where timing allows, for example, the sample may extend over half or more of

the whole of the data. In this way, the total detection time, mass spectrum generation time and decision making time can take less than 100ms. The ion collection and preparation of the very next cycle 150₂ can start as soon as the decision step 160₂ is complete and the ions will be ready for transmission to the ICR cell 120 as soon as the ion detection step 152₁ of the previous cycle is complete.

Furthermore, the ion detection 152 of successive cycles can be performed in parallel, as already described. Likewise, the data processing steps 154 of successive cycles can also be performed in parallel.

This third embodiment shown in Figure 7 is especially useful where the first cycle corresponds to a full mass analysis and the second analysis corresponds to a MS/MS analysis of ions found in the first scan (or any other MSⁿ type of scan). The ability to process a sample of transient data and be in a position to abort full data detection is particularly useful when the ion detection step 152 is far longer than the ion preparation step 150, a typical situation for ultra-high mass resolution experiments. New ions can be generated and detected immediately, for example when a best solution is necessary for monitoring a chromatographic process while still desiring ultra-high resolution.

In a fourth embodiment, the method of the present invention is applied to a hybrid mass spectrometer 110 comprising two detectors, namely a combination of a high-resolution ICR cell 120 and a low-resolution ion detector in the ion storage device 116. Providing the ion storage device 116 with a detector allows not only automatic gain control, but also allows the ion storage device 116 to accumulate and detect ions while the ICR cell 120

collects high-resolution data. The use of previous scans collected by the ICR cell 120 (i.e. the first portion of the detection step) and ion storage device data makes it possible to alter data collection sequences by sending
5 ions to the ICR cell 120 whenever desired, e.g. by interrupting data collection in the ICR cell 120 and injecting further ions. Any chromatogram, or other spectrum, finally determined can contain data mixed from both parts of the hybrid mass spectrometer 110. An
10 example is given in Figure 8, and will now be described.

Ions are accumulated in the ion storage device 116 and detected using a high-speed cycle of 1/10s per mass spectrum. When the chromatographic peak 180 at 10s is detected, the ions are transmitted to the ICR cell 120
15 for an ultra-high resolution scan lasting 10s, as indicated at 182. Meanwhile, further ions are being prepared as detection of ions in the ion storage device 116 continues. At 25s, a new peak 184 is detected in the ion storage device 116, triggering transmission of
20 ions to the ICR cell 120 and the start of a further 10s ultra-high resolution scan as indicated at 184. Continual detection of ions in the ion storage device 116 registers a third peak 186 at 30s. Decision logic operated by the system control computer 130 regards this
25 peak 186 as being more important than the previous peak 184 found at 25s. Consequently, the current ultra-high-resolution scan is aborted at 188 without discarding the data, and the ions are injected into the ICR cell 120 for a third ultra-high-resolution scan 190 to start. All
30 information from all the scans (both the ultra-high-resolution scans from the ICR cell 120 and the low-

resolution scans from the ion storage device) are sent to the store 132, ordered by the time ionisation took place.

This principle is applied in a fifth embodiment of the present invention shown in Figure 9. Ions are
5 prepared in the usual way at 150₁ and are subsequently transmitted to the ICR cell 120 for detection at 152₁. As described before, a preview is generated at 160 using an initial sample of the transient data collected during the ion detection step 152₁. Based on the information gained
10 from the preview 160₁, ions are prepared and stored 200₁ in the ion storage device 116 where one or more data acquisitions are taken 202₁ using the lower resolution detector and stored at 204₁. In this way, ultra-high-resolution scans are collected by the ICR cell 120, while
15 a plurality of MS/MS scans are collected by the ion storage device 116. Once the ICR cell 120 and ion storage device 116 have completed their ion detection steps 152₁, 202₁, a new cycle of ultra-high-resolution and MS/MS scans begins (with parallel processing being
20 possible, as will be evident from the foregoing description).

The person skilled in the art will appreciate that variations can be made to the embodiments described above without departing from the scope of the invention.

25 Whilst the foregoing specific description uses the context of FT-ICR spectroscopy, the present invention is of wider application and may be used in other types of spectroscopy. The present invention will be of particular benefit to types of spectroscopy that involve
30 a data-processing step that requires considerable time. Examples include spectroscopy using quadrapole time of

flight (QTOF), Fourier transform infrared (FT-IR) and nuclear magnetic resonance (NMR).

The present invention is directed to the scheduling of steps within mass spectrometry, and to scheduling with respect to the data collection and processing in particular. As such, the exact details within each step can be varied quite freely. For example, the exact details of the sample preparation, ion generation, ion preparation, ion collection, ion storage and ion transmission are not crucial to the present invention. The same consideration applies to the data collection and data processing steps. For example, the data processing may comprise obtaining a Fourier transform of transient data in order to obtain information regarding the ions. This information may be presented as a frequency spectrum or a mass spectrum, for example.

Most present Fourier transforms (that are used in FT-ICR at least) require the number of data samples to correspond to a power of two. However, fast Fourier transforms may be used that do not have this restriction. This allows for greater freedom in setting the duration of the ion detection step, for example the length may be varied in discrete steps of 50ms or less.

CLAIMS

1. A method of mass spectrometry comprising a plurality
5 of cycles, each cycle comprising the steps of:

(a) preparing ions to be analysed by a mass spectrometer;

(b) using a detector of the mass spectrometer to collect data from the ions prepared in step (a); and

10 (c) processing the data collected in step (b) with processing means;

wherein at least a part of step (a) and/or a part of step (b) of a cycle is performed concurrently with part (c) of a previous cycle.

15

2. A method according to claim 1, comprising the step of starting step (a) of a cycle upon completion of step (b) of the previous cycle.

20 3. A method according to claim 1, comprising the step of starting step (a) of a cycle during step (b) of the previous cycle.

4. A method according to claim 3, comprising the step
25 of starting step (b) of a cycle upon completion of step (b) of the previous cycle.

5. A method according to any preceding claim, comprising the step of controlling step (a) and/or step
30 (b) of a cycle in response to data processed in step (c) of a previous cycle.

6. A method according to any preceding claim, wherein
step (b) further comprises making available a sample of
data collected during an initial period of step (b) for
processing in part (c) while the remainder of the data
5 collection of step (b) continues.

7. A method according to claim 6, comprising the step
of controlling step (a) and/or step (b) of a cycle in
response to a sample of data processed in step (c) of a
10 previous cycle.

8. A method according to claim 7, wherein the mass
spectrometer is a hybrid spectrometer comprising first
and second detectors, the method further comprising the
15 step of injecting ions into the first detector from the
second detector in response to the sample of data
processed in step (c).

9. A method according to claim 8, wherein the first
20 detector is part of an ICR cell and the second detector
is part of an ion storage device.

10. A method of mass spectrometry comprising a plurality
of cycles, each cycle comprising the steps of:
25 (a) preparing ions to be analysed with a mass
spectrometer;
(b) using the mass spectrometer to collect data from the
ions prepared in step (a); and
(c) processing data collected in step (b);
30 wherein a sample of the data collected during an
initial period of step (b) is processed concurrently with
the remainder of the data collection of step (b) and is

used to control step (a) and/or step (b) of a subsequent experiment.

11. A method according to claim 10, wherein the mass
5 spectrometer is a hybrid spectrometer comprising first
and second detectors and wherein the sample of data is
collected in the first detector and, once processed, is
used to control step (a) and/or step (b) of a subsequent
experiment performed with the second detector
10 concurrently with collection of the remainder of the data
by the first detector.

12. A method according to claim 11, comprising the steps
of collecting a full mass spectrometry scan with the
15 first detector and performing a MS^n scan with the second
detector.

13. A method according to claim 11 or claim 12, wherein
at least step (a) and/or step (b) of a cycle is performed
20 concurrently with part (c) of the previous cycle.

14. A method of spectrometry according to any preceding
claim, wherein the mass spectrometry is any one of
Fourier transform ion cyclotron resonance mass
25 spectrometry, Fourier transform Orbitrap mass
spectrometry or quadrupole time of flight spectrometry.

15. A method of mass spectrometry substantially as
described herein with reference to any of Figures 3 to 9.
30

16. A computer program comprising program instructions
operable to carry out the method of any preceding claim.

17. A computer when programmed with the computer program of claim 16.

- 5 18. A computer readable medium having the computer program of claim 15 recorded thereon.

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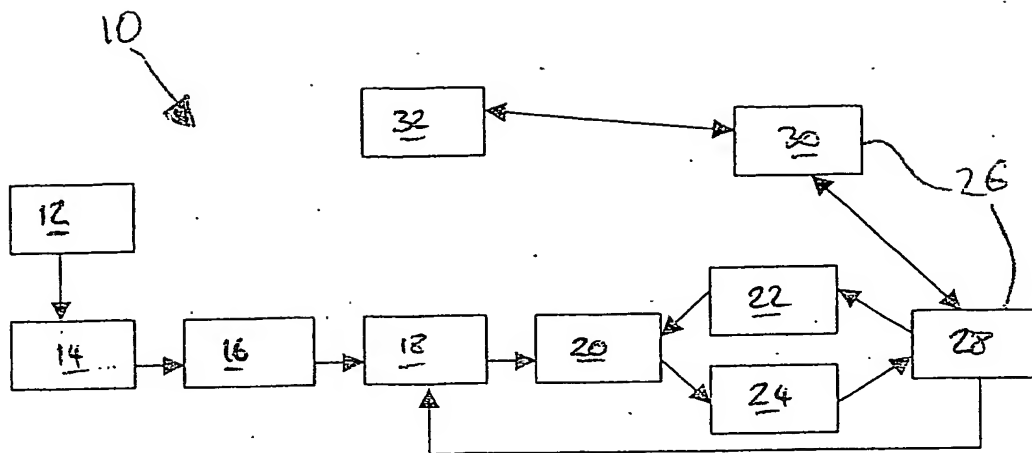


FIGURE 1

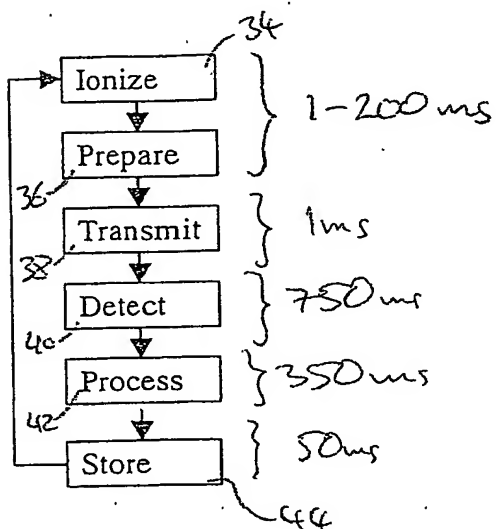


FIGURE 2

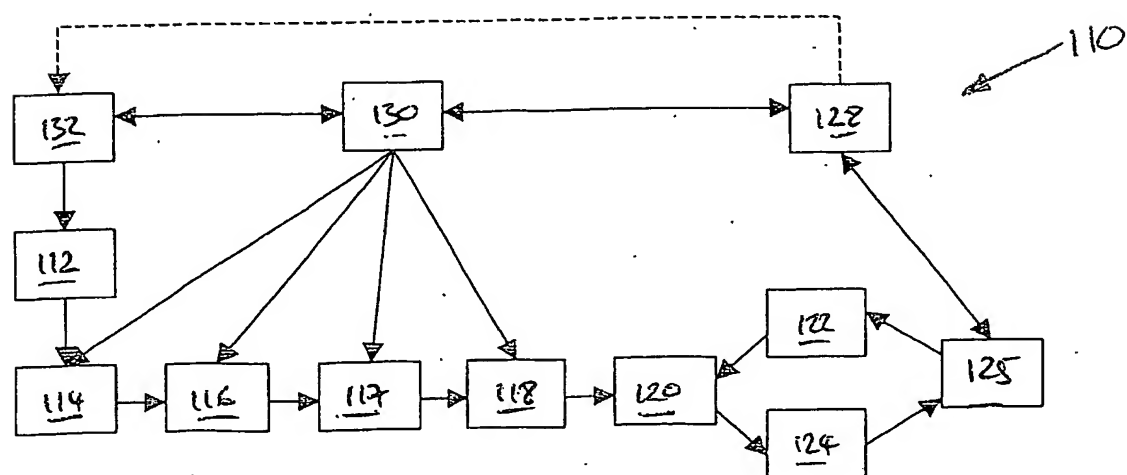
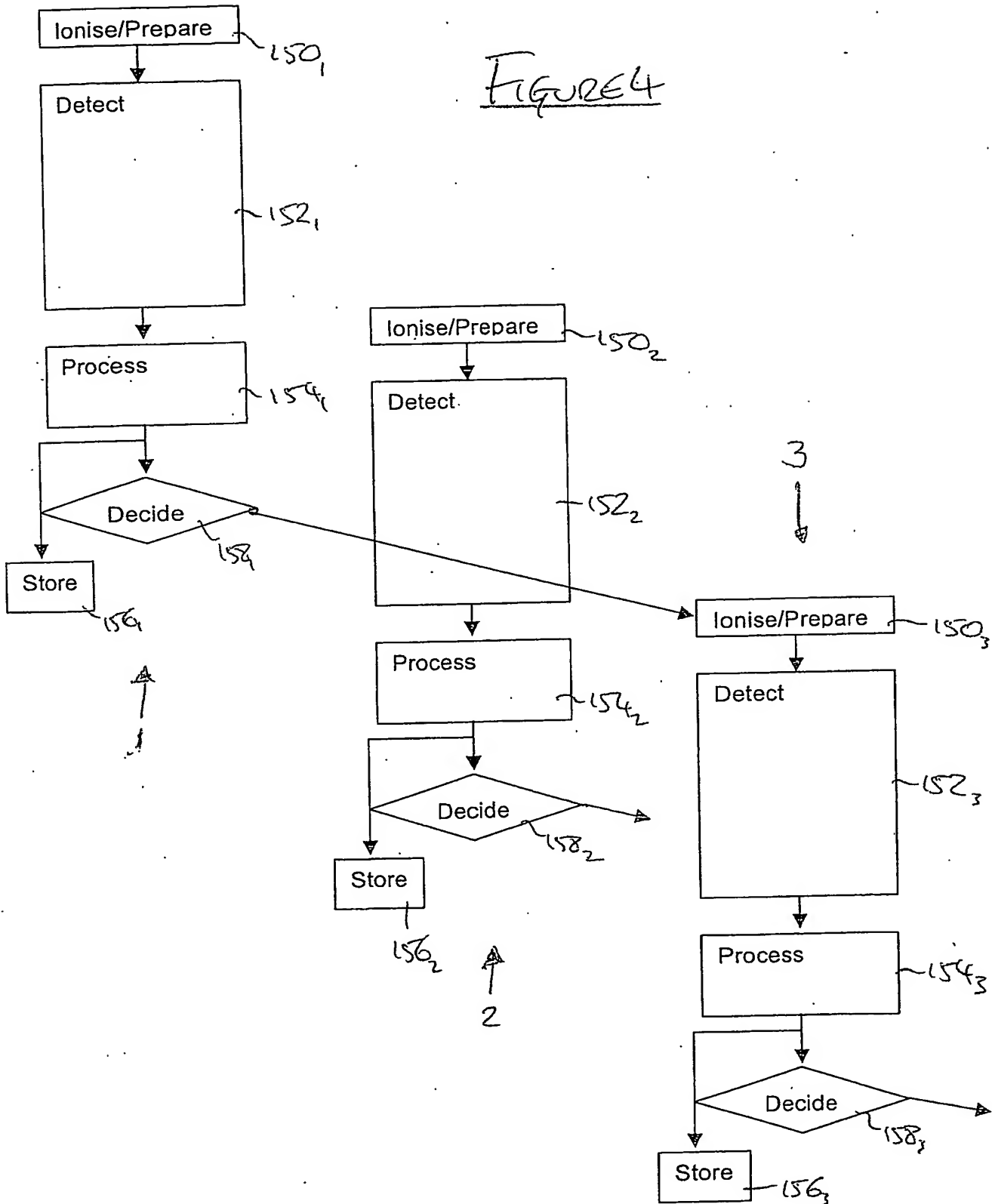
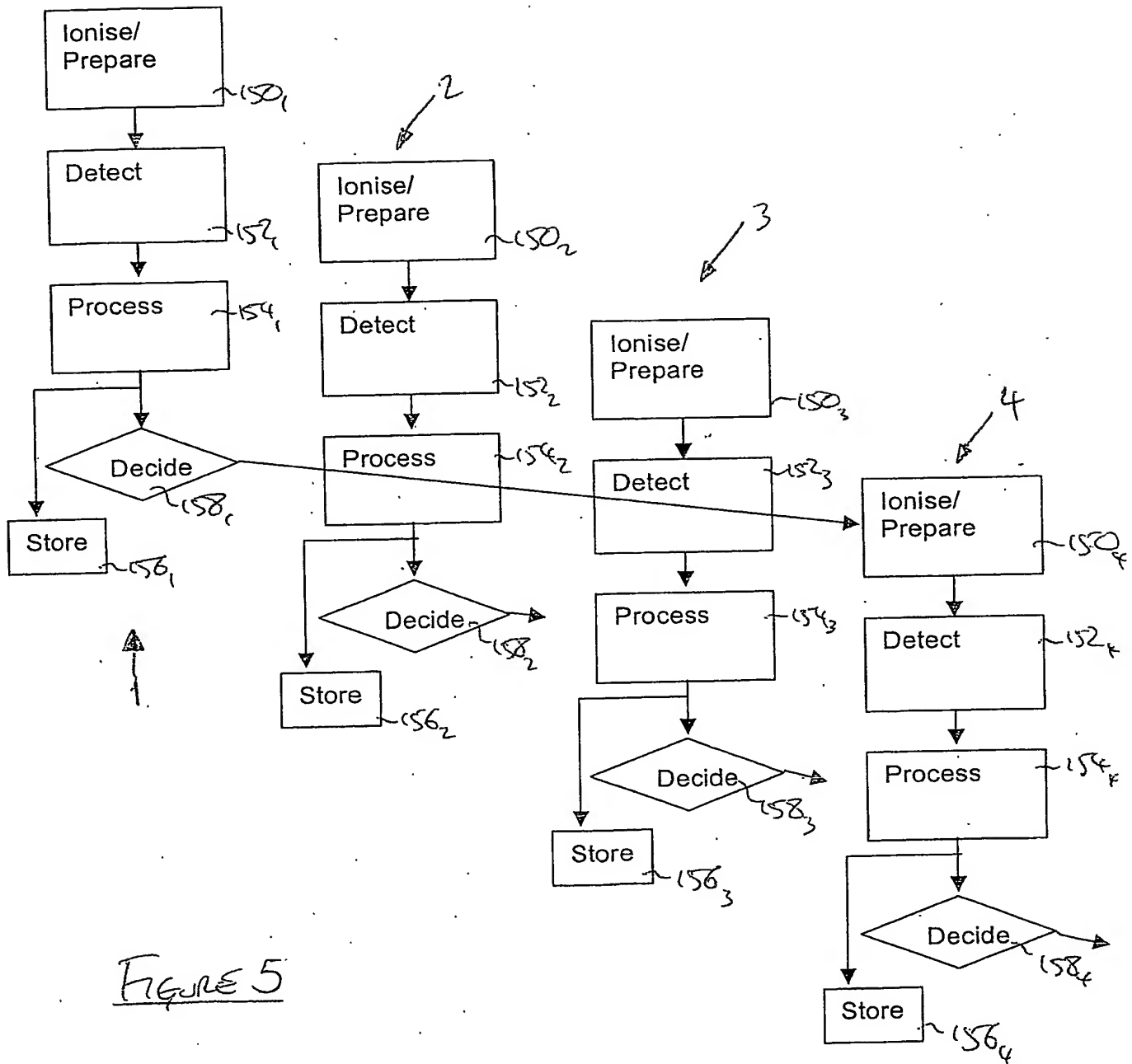


FIGURE 3

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FIGURE 4



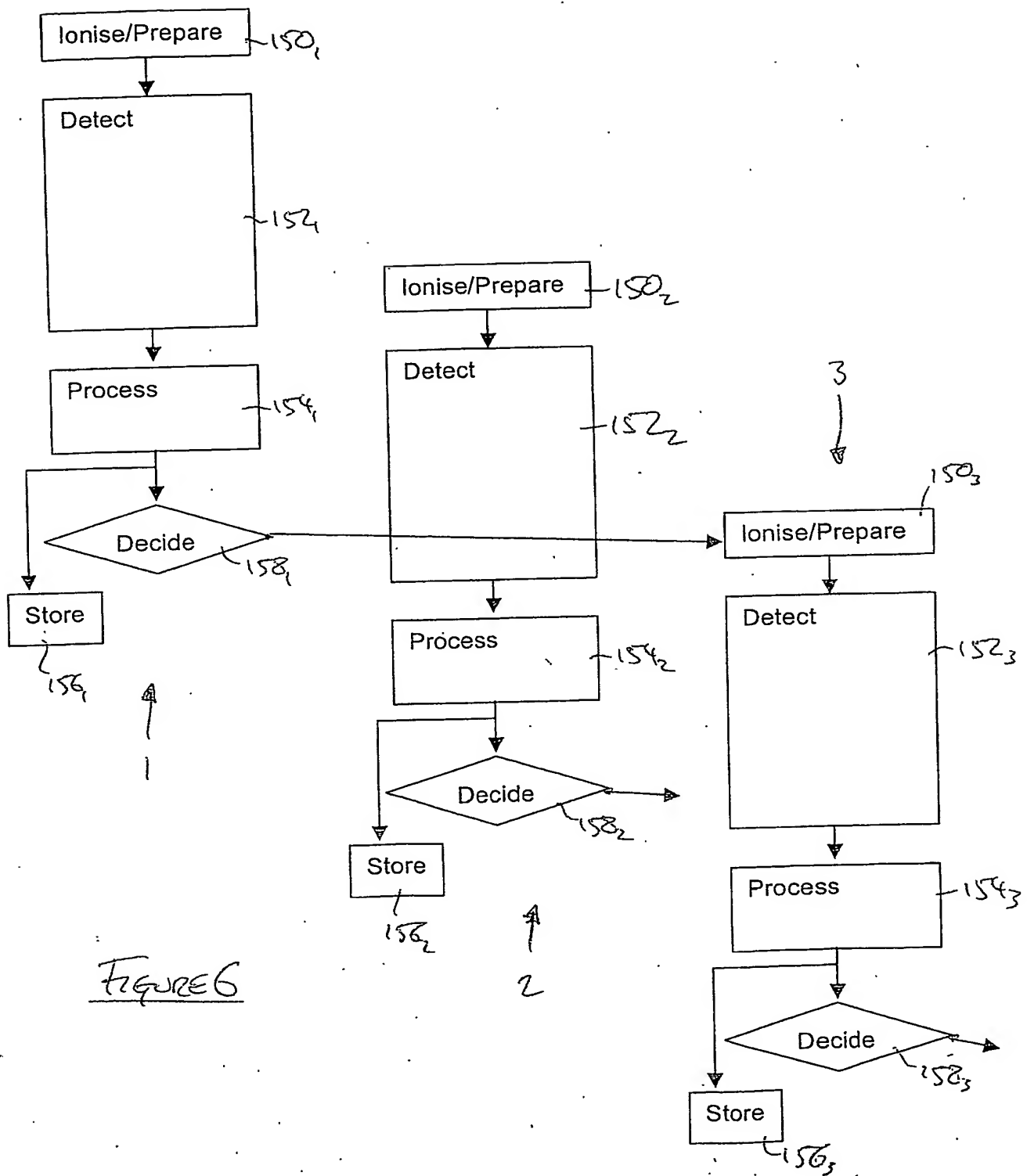
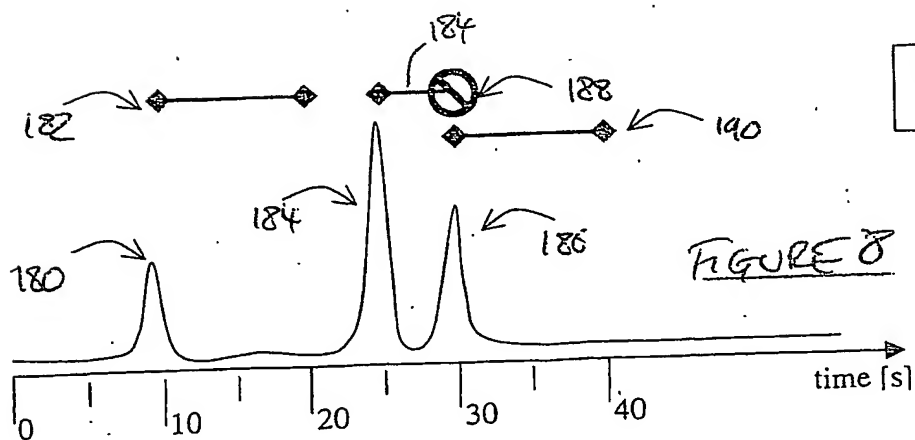
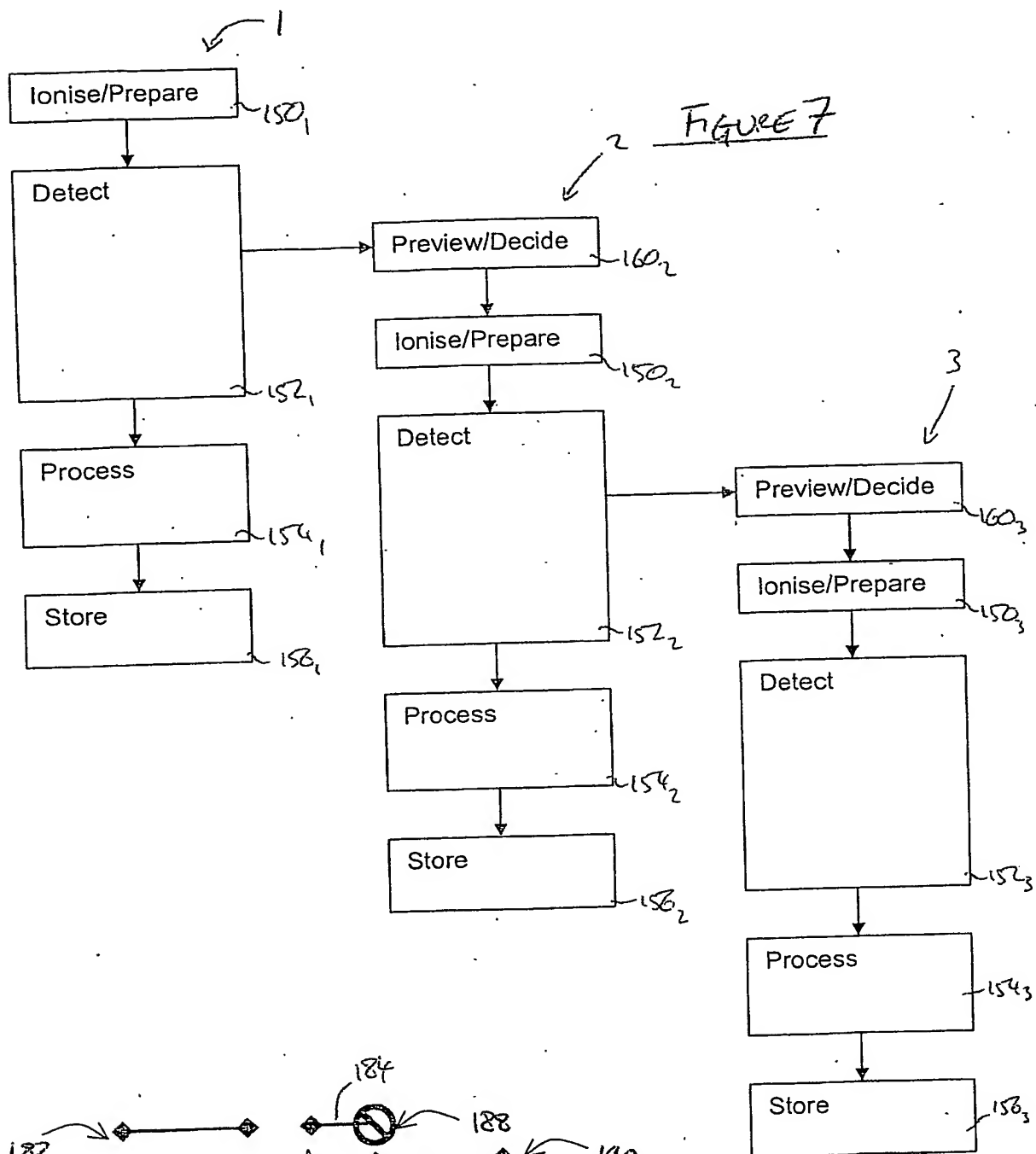


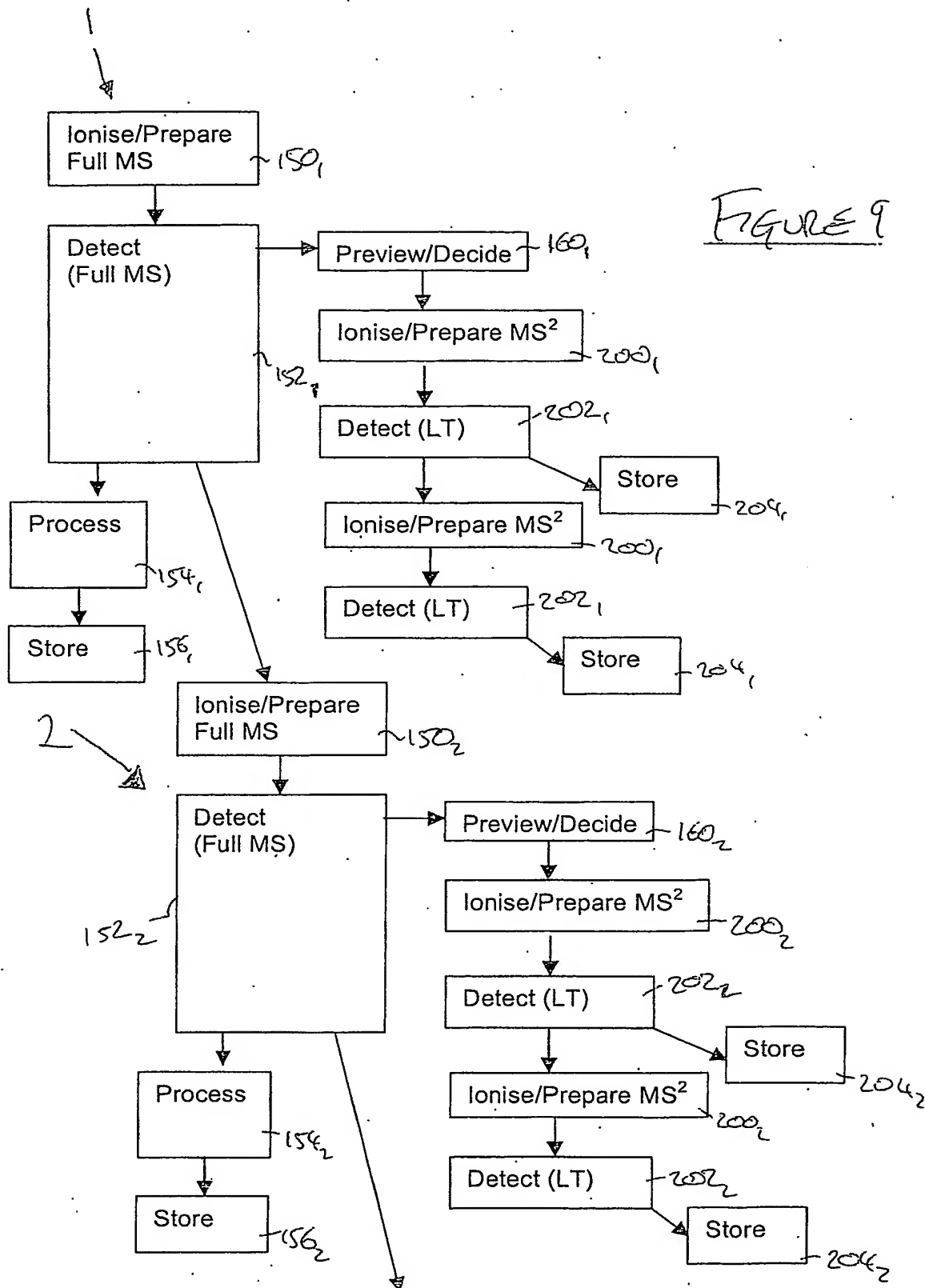
FIGURE 6



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FIGURE 9



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